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Increased spinal pain sensitization:
A new explanation for highly prevalent painful somatic symptoms in major depressive disorder?

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Ce mémoire intitulé:

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A été évalué par un jury composé des personnes suivantes :
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Résumé

Objectifs: Malgré que les patients souffrant de dépression majeure (DM) rapportent souvent des symptômes douloureux, la relation entre la douleur et la dépression n'est pas encore claire. Ce n'est que récemment que des études employant des paradigmes de sommation temporelle ont pu offrir une explication préliminaire de la cooccurrence de la douleur et de la dépression. Notre étude vise à évaluer la contribution des procédés spinaux et surpraspinaux dans la sensibilisation de la douleur dans la DM en utilisant un paradigme de sommation temporelle. **Participants :** Treize sujets sains et quatorze patients souffrant de DM ont été inclues dans l'analyse finale. **Méthodes :** Pour induire une sommation temporelle, nous avons utilisé des stimulations intermittentes du nerf sural de basses et hautes fréquences. La sensibilisation spinale de la douleur a été quantifiée en mesurant la variation de l'amplitude du réflex de retrait nociceptif (NFR) entre les deux conditions de stimulations, ainsi que la sensibilisation supraspinale de la douleur a été obtenue en mesurant le changement dans l'appréciation verbale de la douleur entre ces deux conditions. **Résultats :** Nous avons observé une sensibilisation plus élevée de la réponse NFR chez les patients dépressifs durant la condition de stimulation à haute fréquence, un effet qui n'a pas été reflété par une sensibilisation amplifiée des appréciations subjectives de la douleur durant l'expérience. Néanmoins, nous avons observé une association entre la sensibilisation spinale et les symptômes somatiques douloureux chez les patients DM. **Conclusion :** Ces résultats suggèrent une sensibilisation spinale amplifiée dans la DM, ce qui pourrait expliquer la prévalence élevée des symptômes somatiques douloureux chez ces patients.

Mots-clés : Dépression majeure, douleur, réflex nociceptif, sensibilisation

Abstract

Objectives: Although patients suffering from major depressive disorder (MDD) often complain from painful symptoms, the relationship between pain and depression has yet to be clearly characterized. Only recently have studies employing temporal summation paradigms offered some preliminary insight into the co-occurrence of pain and depression. This study sets out to evaluate the contribution of spinal and supraspinal processes in pain sensitization in MDD using a temporal summation paradigm. **Subjects:** Thirteen healthy controls and fourteen MDD patients were included in the final analysis. **Methods:** To induce temporal summation, we used low- and high-frequency intermittent stimulations of the sural nerve. Spinal pain sensitization was quantified by measuring the change in the amplitude of the nociceptive-specific flexion reflex (NFR) response, and supraspinal pain sensitization was obtained by measuring change in subjective pain rating, from the low- to high-frequency stimulation condition. **Results:** We found an increased sensitization in the NFR response in MDD patients in the high-frequency condition, which did not translate into an increased amplification of their subjective responses during testing. However, we found a positive association between spinal sensitization and painful somatic symptoms in MDD patients. **Conclusion:** Together, these results suggest increased spinal pain sensitization in MDD, which might explain the high prevalence of painful somatic symptoms in these patients.

Key words: Major depressive disorder, pain, nociceptive reflex, sensitization

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CBT : Cognitive-behavioral therapy

dlPFC : Dorsolateral prefrontal cortex

DNIC : Diffuse noxious inhibitory controls

DSM-IV-TR : Fourth edition of the Diagnostic and Statistical Manual of Mental Disorders

DSM-5 : Fifth edition of the Diagnostic and Statistical Manual of Mental Disorders

ECT : Electroconvulsive therapy

EMG : Electromyography

fMRI : Functional magnetic resonance imaging

IASP : International Association for the Study of Pain

ICPM : Inhibitory conditioned pain modulation

MAOIs : Monoamine oxidase inhibitors

MDD : Major Depressive Disorder

MRI : Magnetic resonance imaging

NFR : Nociceptive-specific flexion reflex

NMDA : N-methyl-D-aspartate

NRM : Nucleus raphe magnus

PET : Positron emission tomography

RVM : Rostro-ventral medulla

SES : Socioeconomic status

SNP : Single nucleotide polymorphism

SNRIs : Serotonin-norepinephrine reuptake inhibitors

SSRIs : Serotonin reuptake inhibitors

TCAs : Tricyclic antidepressants

TDCS : Transcranial direct current stimulation

TENS : Transcutaneous electrical nerve stimulation

TMS : Transcranial magnetic stimulation

5-HTR1A : Serotonin 1A receptor gene

5-HTR2A : Serotonin 2A receptor gene

5-HTTLPR : 5-hydroxytryptamine transporter gene

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1 Introduction

1.1 Depression

1.1.1 Epidemiology

With over 350 million people affected worldwide, depression is one of the most prevalent mental health disorder in the general population (Public Health Agency of Canada, 2014) and is currently considered the leading cause of disability by the World Health Organization (WHO, October 2012). The latest Canadian Community Health Survey on Mental Health estimates that 11.3 % of Canadians have experienced symptoms consistent with depression in their lifetime (Pearson et al., 2013), a rate similar to previous estimates from the 2002 Canadian National Survey (Patten et al., 2006). With depression being widespread, many personally face or are impacted by the disorder, hence the necessity to address it.

Across most nations and ethnicities, depression was shown to be twice as prevalent in women than in men (Angst et al., 2002; Kuehner, 2003), a gender difference that emerges in adolescence (Essau et al., 2010; Hyde et al., 2008). The mean age of onset is estimated to be between 25 and 32 years old (Kessler et al., 2005; National Institue of Mental Health, 2015). Having experienced family instability during childhood (Gilman et al., 2003), or being currently separated/divorced increases the risk of developing depression (Andrade et al., 2003). Depression is almost twice as prevalent in high-income countries as in low/middle - income countries (Bromet et al., 2011). Conversely, in high income countries, depression is more frequently reported among people of lower socioeconomic status (SES) (Lorant et al., 2003). In fact, lower SES during childhood (Gilman et al., 2002), and worsening SES (Lorant et al., 2007) were associated with increasing rates of depression. Unfortunately, a poorer SES

has not only been linked with poor mental health, but with poor physical health as well (Everson et al., 2002).

1.1.2 Consequences

In a comprehensive review of epidemiological studies, Evans et al. (2005) detail the extensive repercussions of depression on medical conditions, which include among others an increased risk of cardiac disease (Rudisch & Nemeroff, 2003), diabetes (Musselman et al., 2003), a perturbation of recovery from cerebrovascular diseases (Krishnan, 2000), a higher cancer mortality rate (Satin et al., 2009), poor human immunodeficiency virus and acquired immune deficiency syndrome treatment adherence (Gonzalez et al., 2011), and an increased severity of chronic pain (Arnow et al., 2006). The consequences of this disorder are manifested as well in socio-professional functioning impairments (Kessler et al., 2003) and an overall diminished quality of life (IsHak et al., 2015).

Depression is also a public health issue, with absenteeism (Druss et al., 2000), loss of productivity (Stewart et al., 2003), and a substantial increase in costs related to medical resource consumption (Luppa et al., 2007) as some of the disorder's economic implications. With 33 % of total costs related to brain disorders in Europe attributable to depression (Sobocki et al., 2006), and ranking in sixth place in terms of economic costs in an international review (Berto et al., 2000), depression indubitably constitutes both a great individual and societal burden.

An important concern regarding this disorder is the 52 percent greater risk of mortality in depressed individuals compared to the general population (Cuijpers et al., 2014). Other than the negative influence of depression on other medical illnesses which can offer a partial explanation, more than half of suicide victims are thought to suffer from depression

(Cavanagh et al., 2003). Furthermore, depressed individuals are at 2.6 fold higher risk of death by homicide (Crump et al., 2013b), and at 2 fold higher risk of accidental death (Crump et al., 2013a).

1.1.3 Clinical features

To be diagnosed with Major Depressive Disorder (MDD) according to the recent fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013a), an individual has to meet/display five or more of the following nine signs or symptoms continuously for a period of at least two weeks: a) depressed mood, most of the day as indicated by subjective reports or observations made by others; b) diminished interest or pleasure in most activities, most of the day; c) significant weight change, including weight loss when not dieting or weight gain, or change in appetite, increase or decrease; d) change in sleep, insomnia or hypersomnia; e) change in activity, as manifested by psychomotor agitation or retardation observable by others; f) fatigue or loss of energy; g) feelings of worthlessness or excessive or inappropriate guilt; h) diminished ability to think or concentrate, or more indecisiveness as indicated by subjective reports or observations made by others; and i) recurrent thoughts of death, or suicidal ideation without a plan, or suicidal ideation with a specific plan, or a suicide attempt. The symptoms have to cause clinically significant distress or impairments in functioning, as well as the episode should not be attributable to the effects of a substance or another medical condition.

The DSM-5 criteria for MDD remain, for the most part, unchanged from the definition of the previous fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (American Psychiatric Association, 2000). However, the bereavement exclusion in the DSM-IV-TR, which specified that individuals presenting depressive

symptoms lasting less than 2 months after the death of a loved one did not meet the diagnostic criteria for MDD, was removed from the DSM-5. Evidence showed that depressive symptoms emerging as a consequence of bereavement were not different from those caused by other stressors (American Psychiatric Association, 2013b).

Although only 2 symptomatic weeks are necessary for the diagnosis of MDD, the median duration of a depressive episode was observed to vary between 3 to 6 months in large cohort studies (Eaton et al., 2008; Richards, 2011). Following the first episode of MDD, close to half of MDD patients were found to recover with no relapse (Eaton et al., 2008). It is estimated that 15 % to 42 % of MDD patients will experience the recurrence of the disorder within 20 years following a depressive episode (Eaton et al., 2008; Hardeveld et al., 2013). Additionally, the risk of a subsequent depressive episode increases with each recurrence of a depressive episode (Solomon et al., 2000).

An important issue with diagnosing MDD is the difficulty of differentiating core MDD symptoms from symptoms specific to other psychiatric disorders because of the often significant overlap. It is estimated that half of the individuals suffering from bipolar disorder have a depressive episode before the manifestation of manic symptoms (Etain et al., 2012), as well as patients suffering from bipolar disorder were shown to be more likely to consult for depressive symptoms than for manic symptoms (Hirschfeld, 2004). Furthermore, generalized anxiety disorder and MDD share a number of somatic symptoms (Zbozinek et al., 2012), and depressive mood is very common in prodromal schizophrenia (Hafner et al., 2005). Taking into account the overlap of symptoms is definitely crucial when establishing a MDD diagnosis.

1.1.4 Etiology

Similar to other psychiatric disorders, the consensus is that a gene x environment interaction is involved in the etiology of MDD. An estimated third of the risk for developing depression is attributed to genetic factors (inherited) and two-thirds of the risk to environmental factors (Sullivan et al., 2000). In line with the gene x environment interaction, much of the theories describing MDD follow a diathesis-stress model (Willner et al., 2013), where the vulnerability (diathesis) of an individual for MDD can be precipitated by adverse life events (stress). Complementary to this model, stress-inflammation pathways have been proposed as potential underlying processes in depression (Saveanu & Nemeroff, 2012), where stress induced immune response may play a role in the pathogenesis of MDD (Slavich & Irwin, 2014). Psychosocial stress originating from interpersonal, legal, or work related events (Brigitta, 2002), stress from the aftermath of a major trauma (O'Donnell et al., 2004), or the loss of loved ones (Zisook & Shuchter, 1991) were reported as some of the potential sources that might trigger the onset of MDD. Stressful events and physical or sexual abuse in childhood were shown to increase the predisposition of an individual towards developing the disorder (Saveanu & Nemeroff, 2012).

Twin studies have been consistent in demonstrating the moderate heritability of MDD (Kendler et al., 2006; Kendler & Prescott, 1999), yet the genetic basis of the disorder has proven to be difficult to define. The Genome Wide Association Study conducted by the Cross-Disorder Group of Psychiatric Genomics Consortium (Lee et al., 2013) found a shared genetic etiology for attention deficit hyperactivity disorder, bipolar disorder, schizophrenia, depression and autism. This might be in part the consequence of overlapping or broad symptoms, and

heterogeneous disorders. Nonetheless, studies have succeeded to a certain extent in supporting specific neurobiological mechanisms underlying MDD with genetics.

1.1.5 Neurobiology

The monoamine deficiency hypothesis, a popular neurobiological model of depression, was developed to explain the efficacy of monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) in treating MDD patients (Hindmarch, 2001). Considering that both MAOIs and TCAs facilitate monoamine neurotransmission in the brain (Hindmarch, 2001), the model postulates that monoamine neurotransmitters are depleted in MDD (Delgado, 2000), especially: serotonin and norepinephrine. The serotonergic system, involved in impulsivity and vigilance, originates in the raphe nuclei of the brainstem and projects to a wide area in the brain, including the frontal cortex, limbic system (amygdala and hippocampus), and hypothalamus (Savitz & Drevets, 2009). Similarly, the noradrenergic system originates in the brainstem (locus coeruleus) and projects diffusely across the brain to the prefrontal cortex, thalamus, hypothalamus, hippocampus, and amygdala; it is, however, associated to arousal and stress response (Goddard et al., 2010). Overall, the anatomy of the monoaminergic systems suggest they are involved in the regulation of a broad spectrum of behaviors and brain functions, such as mood, attention, motivation, psychomotor agitation, sleep, appetite and cognition (Brigitta, 2002; Hasler, 2010).

Human studies in genetics and positron emission tomography (PET) imaging have provided partial support to the monoamine hypothesis, particularly with regards to the implication of serotonergic neural transmission abnormalities in the pathophysiology of depression. Notably, the less functional short (s) allele variation in the 5-hydroxytryptamine transporter gene (5-HTTLPR) polymorphic promoter region, associated with lower serotonin

transporter protein expression than the long (l) allele, was repeatedly linked with increased risk for MDD in response to adverse life events (Daniele et al., 2011; Karg et al., 2011). Consistent with these findings, studies in PET observed lower serotonin transporter density in the brain of depressed suicide attempters (Miller et al., 2013), and medication-free MDD patients (Selvaraj et al., 2011), also mirroring post-mortem results suggesting decreased serotonin transporter density in depressed suicide victims (Stockmeier, 2003). However, in both PET imaging and post-mortem studies, these results appear to be related to suicidal behavior more so than depression (Miller et al., 2013; Stockmeier, 2003). Furthermore, certain PET studies observed the opposite relation between serotonin transporter binding and MDD (Cannon et al., 2007), or failed to find an association (Meyer et al., 2004). In turn, serotonin receptors have been associated to MDD with similarly mixed results. A single nucleotide polymorphism (SNP) located in the serotonin 1A receptor gene (5-HTR1A) promoter region, associated with increased expression of the 5-HTR1A receptor, was significantly associated with mood disorders (Kishi et al., 2013). However, PET studies investigating the 5-HTR1A receptor density in MDD patients have either found that MDD was associated with decreased binding potential (Savitz & Drevets, 2009), or were inconclusive (Shrestha et al., 2012). SNPs in the promoter region of the serotonin 2A receptor gene (5-HTR2A) have been inconsistently linked with MDD, with meta-analyses reporting an association between certain SNPs and depression (Zhao et al., 2014), and no relationships with other SNPs (Jin et al., 2013).

The involvement of the noradrenergic system in the pathophysiology of depression has received some attention as well, albeit to a lesser extent (Moret & Briley, 2011). Although reduced levels of norepinephrine transporters were found in the locus coeruleus of MDD patients post-mortem (Klimek et al., 1997), no associations between MDD and SNPs in the

promoter region of the norepinephrine transporter gene were observed in a short meta-analysis (Zhao et al., 2013). Increased α2- and β1-adrenoceptor densities were reported in post-mortem brain of MDD suicide victims (Rivero et al., 2014), which is in line with the monoamine hypothesis (Goddard et al., 2010), although the evidence is limited. Overall, studies in genetics and PET imaging investigating the monoamine hypothesis of MDD remain for the most part inconclusive.

Recently, the involvement of the glutamatergic system in the pathophysiology of depression has received considerable attention (Mitchell & Baker, 2010), motivating a number of studies to investigate the prophylactic effect of low-dose ketamine, targeting N-methyl-D-aspartate (NMDA) receptors, in treating symptoms of depression (Aan Het Rot et al., 2012). Although most compelling evidence for the implication of the glutamatergic system in MDD comes from clinical trials with glutamatergic agents such as ketamine, there are preliminary results in post-mortem and magnetic resonance spectroscopy studies in humans suggesting a decrease/dysregulation of glutamate metabolites in the prefrontal cortex and the limbic system of individuals suffering from MDD (Mitchell & Baker, 2010). Because of both the limited and delayed effect of current monoamine treatments in MDD, the complementary role of glutamate, which is not a monoamine neurotransmitter, appears to be worthwhile to pursue in future research.

Studies in magnetic resonance imaging (MRI) and functional MRI (fMRI) have identified brain regions that may be implicated in the neurobiology of MDD. One of the most consistently documented result in MDD is the increased reactivity of the amygdala in response to negative stimuli compared to healthy individuals (Hamilton et al., 2012), an effect that has been associated to the s allele of the 5-HTTLPR gene (Savitz & Drevets, 2009). The insula

and the dorsal anterior cingulate cortex were also shown to be overactive in response to negative stimuli in MDD patients (Hamilton et al., 2012), thereby indicating the potential involvement of hyperactive (para)limbic structures in the pathophysiology of MDD. Conversely, studies found negative stimuli to elicit decreased response in the dorsolateral prefrontal cortex (dlPFC) and the dorsal striatum in MDD (Hamilton et al., 2012), results that are corroborated by studies suggesting a disrupted fronto-limbic connectivity in depression (Savitz & Drevets, 2009). Given the implication of the dlPFC in cognitive control/ inhibition, these results support the cognitive model that posits a deficit in the regulation of emotional processing in MDD (Gotlib & Joormann, 2010; Wolkenstein & Plewnia, 2013). The role of the hippocampus in MDD has also received some attention, as biased memory processes towards negative stimuli have been reported in MDD (Gotlib & Joormann, 2010), and fMRI studies have observed less recruitment of this region during memory tasks in depressed patients compared to healthy individuals (Milne et al., 2012). Reduced hippocampal gray matter volumes were also observed in MDD patients, which might potentially be explained by decreased hippocampal neurogenesis (Eisch & Petrik, 2012). Authors hypothesize that these functional and structural changes in the hippocampus of MDD patients might be involved in the pathophysiology of MDD (Campbell & Macqueen, 2004). Further abnormalities have been identified in the brain morphology of MDD patients, including gray matter reductions in the limbic regions (anterior cingulate cortex), frontal regions (middle and frontal gyrus), and the thalamus (Du et al., 2012).

1.1.6 Treatment

According to the National Health and Nutrition Examination Surveys in the United States, up to 11 % of Americans are prescribed antidepressants, making it the third most common

prescription drug in the U.S. (Pratt et al., 2011) and amounting to an estimated 11 billion dollars in spending in 2011 (Institute for Healthcare Informatics, April 2012). Even though antidepressants are also used to treat other disorders, which might explain the elevated costs, pharmacotherapy seems to be the preferred treatment for MDD. Although the efficacy might vary depending on the severity of the depression (Kirsch et al., 2008), antidepressants have only shown modest efficacy compared to placebo treatments (Lima & Moncrieff, 2000; von Wolff et al., 2013), with less than 50 % of MDD patients achieving adequate response to treatment with antidepressants (Fava, 2003).

Currently, there are over five classes of antidepressants prescribed to MDD patients. MAOIs, the first class of antidepressants that was developed, inhibit the activity of the monoamine oxidase enzyme involved in the catabolism of monoamines such as serotonin, noradrenaline and dopamine (Shulman et al., 2013). By inhibiting their breakdown, MOAIs increase the availability of monoamine neurotransmitters in the brain. TCAs and tetracyclic antidepressants, the second class of antidepressants, exert their effect by inhibiting the reuptake of serotonin and norepinephrine from the synaptic cleft, thereby increasing the availability of those neurotransmitters (Hindmarch, 2001). Together, cyclic antidepressants and MAOIs constitute the first-generation of antidepressant medication, which led to the advent of the monoamine-deficiency hypothesis in MDD. Of the second-generation antidepressants, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have similar mechanisms of action, where both selectively block the reuptake of serotonin and/or norepinephrine and have little affinity to histamine and muscarinic receptors (Horst & Preskorn, 1998), the latter being potentially the reason why these second generation antidepressants have less side-effects than MAOIs and TCAs.

Because they increase synaptic availability of monoamines, the efficacy of SSRIs and SNRIs in MDD corroborates the monoamine-deficiency hypothesis. Moreover, the efficacy of SSRIs in MDD has been associated with serotonin transporter gene promoter polymorphisms (Porcelli et al., 2012; Serretti et al., 2007). Further second-generation antidepressants include atypical antidepressants, which are more tolerable than first-generation antidepressants despite having multiple sites of actions (Horst & Preskorn, 1998).

Likewise, there are many psychotherapies that are employed to treat MDD patients. Out of the common therapies, which include cognitive-behavioral therapy (CBT), nondirective supportive treatment, behavioral activation treatment, psychodynamic treatment, problem-solving therapy, interpersonal therapy, and social skills training, meta-analyses indicate that there is little difference between the efficacy of these psychotherapies (Barth et al., 2013; Cuijpers, van Straten, Andersson, et al., 2008), yet most studies agree that interpersonal psychotherapy (Schramm et al., 2007) and cognitive-behavioral therapy (Luty et al., 2007) are the most efficacious. Physical exercise is also often recommended to MDD patients, and has shown similar efficacy to the above mentioned therapies (Cooney et al., 2013). Nondirective supportive treatment is, however, less efficacious than the other available therapies (Cuijpers, van Straten, Andersson, et al., 2008). Overall, pharmacotherapy and psychotherapy individually appear to be equally effective (Cuijpers, van Straten, van Oppen, et al., 2008), and Cuijpers et al. (2012) recommend a combination of pharmacotherapy and psychotherapy, as it results in better outcome than any individual therapy.

There are few alternatives to pharmacotherapies and psychotherapies, namely somatic therapies (Cusin & Dougherty, 2012). Although mostly used for acute refractory depression, a recent meta-analysis reported a 50.9 % remission rate in unipolar depression using

electroconvulsive therapy (ECT) (Dierckx et al., 2012). In ECT, bifrontal electrode placement was found to elicit less of the cognitive impairments previously reported with ECT, such as memory loss, while remaining as efficacious as other electrode placements (Bailine et al., 2000). Interestingly, electrical stimulation of the frontal brain regions using transcranial direct current stimulation (TDCS) resulted in enhanced cognitive control in MDD patients (Wolkenstein & Plewnia, 2013), which the authors attributed to the activation of the hypoactivated dlPFC that is characteristic of MDD (Hamilton et al., 2012). Studies using transcranial magnetic stimulation (TMS) have also focused on activating and/or inhibiting the dlPFC in MDD patients with the same purpose as TDCS (Cusin & Dougherty, 2012), although remission rates from MDD using TMS are lower than treatments employing ECT (Carpenter et al., 2012).

1.2 Pain

1.2.1 Epidemiology

Primarily an adaptive multidimensional sensory experience providing relevant information for the protection of the organism from injury, and promoting healing when injury has occurred, pain can become a disease when it is maladaptive and/or chronic (Woolf, 2004). An estimated 20 % of adults report experiencing pain (Goldberg & McGee, 2011), and between 10 % and 19 % of adults, representing more than 1.5 million Canadians and 39.4 million Americans, suffer from chronic/persistent pain according to Canadian and U.S. national health surveys (Kennedy et al., 2014; Ramage-Morin & Gilmour, 2010; Reitsma et al., 2011). Pain is a major health care concern, as it accounts for 20 % of medical consultations (Alford et al., 2008) and between 4 and 6 billion dollars in direct costs in Canada (Lynch et al., 2009; Philips &

Schopflocher, 2008). Chronic pain has been linked with increased absenteeism, lost productivity at work, as well as interference with daily activities (Reitsma et al., 2011). Higher chronic pain prevalence was associated with sex (women), increasing age, marital status (separated/divorced), and lower SES (Johannes et al., 2010). Although predominantly perceived as a symptom rather than a disease (Goldberg & McGee, 2011), pain and chronic pain have received increasing attention due to their extensive impact on both patients and health care system.

1.2.2 Clinical features

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (IASP, 2012a). Chronic pain is characterized as pain that may arise from injury, or manifest itself without clear cause, and last longer than 3 to 6 months (American Psychiatric Association, 2013a; IASP, 1986; National Institute of Health, 2011). Both acute and chronic pain are multi-facetted experiences of heterogeneous aetiologies (Woolf, 2004).

Pain experience can be divided into three psychological dimensions: sensory-discriminative, affective-motivational and evaluative-cognitive (Melzack & Casey, 1968). The sensory-discriminative aspect of pain refers to the intensity, duration, location and quality of the pain experienced. The affective-motivational aspect of pain refers to the unpleasantness of pain and the urge towards escaping the unpleasantness or attacking its source. The intensity of the pain experienced along the sensory-discriminative and affective-motivational dimensions are influenced by the central evaluative-cognitive dimension, which refers to the appraisal of the input from the first two dimensions based on past experiences.

Pain is commonly divided into four distinct types of pain: nociceptive, inflammatory, neuropathic, and functional (Marchand, 2008; Woolf, 2004). Nociceptive pain is the transient response to noxious stimuli indicating the presence of damaging or potentially damaging stimuli. Following an injury, inflammatory pain can be experienced as an increased sensitivity to the affected area which prevents contact or movement of the injured part, in order to promote healing. Neuropathic pain is the consequence of lesions or diseases to the peripheral nervous system. Lastly, functional pain occurs in the absence of detectable lesions or abnormalities. This latter type of pain may occur as a result of abnormal responsiveness of the nervous system.

1.2.3 Physiology

Nociception is the encoding of noxious stimuli in the nervous system (IASP, 2012a; Loeser & Treede, 2008). It is initiated by nociceptive stimuli, which are damaging or potentially damaging mechanical, thermal or chemical events (IASP, 2012b; Mitra et al., 2013), activating nociceptors, which are specialized sensory free nerve endings, located in peripheral tissues responding almost exclusively to pain stimuli (Woolf, 2004). Nociceptor terminals transduce noxious stimuli into action potentials, that are then conducted along primary afferent fibers from peripheral terminals through the dorsal root ganglion, entering the spinal cord via the dorsal root, to finally reach the central nervous system (Mitra et al., 2013; Woolf, 2004).

There are two distinct types of peripheral afferent fibers that carry pain sensation: myelinated Aδ-fibers and thinly/un-myelinated C-fibers (Woolf, 2004). Afferent fibers with myelinated axons (Aδ-fibers) have rapid conduction velocity, and are therefore responsible for the immediate transient sharp pain sensation, or first pain sensory input (Marchand, 2008). Afferent fibers with unmyelinated axons (C-fibers) constitute approximately 75 % of

peripheral fibers, and have slow conduction velocity (Marchand, 2008). C-fibers are responsible for the delayed and prolonged diffuse dull pain sensation, or second pain sensory input (Mitra et al., 2013). Both Aδ-fibers and C-fibers (first order neurons) transport the information from the affected area to the spinal cord. On the other hand, non-noxious sensations, including vibration, movement and light touch, are carried from the periphery to the spinal cord by large myelinated Aα-fibers and Aβ-fibers, which have faster conduction velocity than Aδ-fibers (Marchand, 2008).

Peripheral afferent fibers synapse in the dorsal horn of the spinal cord, where the signal may be modulated via synaptic contact with inhibitory and excitatory interneurons before being transmitted to second order neurons (Woolf, 2004). Second order neurons project from the dorsal horn of the spinal cord to supraspinal systems through two separate ascending pathways: the sensory spinothalamic tract and the affective spinoreticulothalamic/ spinoreticular tract (Basbaum et al., 2009; Marchand, 2008).

Only a fraction of the input from nociceptors will be transmitted to the thalamus, and then relayed to the cortex by third order neurons (Woolf, 2004). The spinothalamic tract projects directly from the dorsal horn of the spinal cord to the contralateral nuclei of the ventrobasal thalamus (Marchand, 2008). From the thalamus, the information is then transmitted to the somatosensory cortex as well as (para-)limbic regions (Marchand, 2008). The projection neurons in the spinothalamic tract have fast conducting axons, small receptive fields, as well as somatotopic organization (Hong et al., 2011) making this pathway essential for the sensory-discriminative aspects (location, duration and intensity) of pain (Basbaum et al., 2009). The spinoreticular tract projects from the dorsal horn of the spinal cord to the reticular formation which in turn projects to the medial nuclei of the thalamus (and then to the

primary somatosensory cortex), the hypothalamus and the limbic system (Patestas & Gartner, 2009). The projection neurons in this latter tract have large receptive fields and are essential in the affective-evaluative aspects (emotional and memory) of pain (Mitra et al., 2013). From the dorsal horn, the spinoreticular tract also projects to the periaqueductal gray (PAG) area and the nucleus raphe magnus (NRM) located in the brainstem (Marchand, 2008).

Studies in PET and fMRI have shown a distributed network of cortical structures participating in pain perception (Marchand, 2008). The primary somatosensory cortex and secondary somatosensory cortex are believed to be involved in the sensory-discriminative aspects of pain (Ossipov, 2012; Peyron et al., 2000), whereas the anterior cingulate cortex, the insula (Apkarian et al., 2005), as well as the amygdala (Simons et al., 2014) are thought to be involved in the affective-emotional aspects of pain. Finally, the prefrontal cortex may be involved in the cognitive-evaluative aspects of pain perception (Apkarian et al., 2005), such as the modulation of the intensity of the pain subjectively perceived through the reappraisal of the painful stimuli (Wiech et al., 2008). Specifically, fMRI studies examining the influence of cognitive processes on pain perception have shown that regions in the prefrontal cortex such as the orbitofrontal cortex (Bantick et al., 2002), dlPFC (Lorenz et al., 2003), and the ventrolateral prefrontal cortex (Wiech et al., 2008) potentially exert control on the activity of regions responsible for the affective-emotional qualities of pain (e.g. amygdale, insula).

1.2.4 Endogenous inhibitory pain modulation

The ascending nociceptive pathways describe the way in which the nociceptive signal is transmitted from the periphery to the central nervous system. However, nociception and pain perception are separate processes, as the afferent nociceptive signal can be modulated by inhibitory and excitatory mechanisms before being perceived by the organism (Marchand,

2008). These endogenous mechanisms modulating the nociceptive signal are categorized into spinal, descending and supraspinal processes.

The inhibitory modulation of nociceptive input at the spinal cord was first described by Melzack and Wall (1965) in the gate control theory of pain, and has been well document since then (Marchand, 2008). The theory asserts that non-nociceptive peripheral input can suppress nociceptive signal from travelling to the central nervous system (Melzack & Wall, 1965). The input from non-nociceptive Aα-fibers and Aβ-fibers in the dorsal horn of the spinal cord will recruit inhibitory interneurons in the substantia gelatinosa, producing localized analgesia, thereby limiting or preventing the transmission of afferent nociceptive signal from Aδ and C fibers to second order neurons (Calvino & Grilo, 2006). Transcutaneous electrical nerve stimulation (TENS) is a clinical application of the gate control theory of pain, as it employs electrical stimulations applied to the skin to relieve pain (Sluka & Walsh, 2003).

A growing number of supraspinal processes influencing descending inhibitory mechanisms have been reported in the literature. Descending inhibitory mechanisms from the brainstem were described by Lebars et al. (1979) as diffuse noxious inhibitory controls (DNIC). Lebars et al. (1979) postulated that a nociceptive stimulation will inhibit another spatially distant nociceptive stimulation by producing diffuse analgesia throughout the rest of the body (i.e. counter-irritation) (Marchand, 2008). Studies showed that DNIC recruit opioids in the PAG, therefore triggering the release of serotonin from rostro-ventral medulla (RVM) neurons. The release of serotonin decreases the input from nociceptive afferent fibers at the dorsal horn of the spinal cord (Stavro & Potvin, 2014). Noradrenergic projections from the locus coeruleus were shown to produce similar descending inhibitory effects (Ossipov et al., 2010). Notably, a deficit in inhibitory conditioned pain modulation (ICPM) (Yarnitsky, 2010),

a term referring to DNIC in human experimental setting, was shown to be a key element in chronic pain disorders, such as fibromyalgia (Marchand, 2008).

Other supraspinal inhibitory mechanisms have also been reported, involving prefrontal and limbic brain activity in particular. Multiple supraspinal processes, including cognitive modulators such as attention (i.e. distraction), reappraisal, hypnosis (i.e. suggestion), and placebo analgesia (Marchand, 2008; Wiech et al., 2008), were shown to inhibit pain perception. Studies in brain imaging have suggested that these cognitive factors exert their analgesic effect by recruiting prefrontal regions, which in turn inhibit brain regions that are involved in the emotional component of pain (Ochsner & Gross, 2005). In addition to these cognitive factors, positive and agreeable emotions induced by music, odors or films (Roy et al., 2008) were found to have analgesic properties as well. Preliminary studies in fMRI suggest that the analgesic effect might be produced by recruiting the reward system (e.g. ventral striatum) (Schweinhardt et al., 2009).

1.2.5 Endogenous excitatory pain modulation

The excitatory modulation of spinal cord neurons can be distinguished in two separate, albeit related, mechanisms: windup and central sensitization (Woolf, 2011). Windup consists of a progressive increase in action potential discharge in second order neurons during high-frequency (≥0.3 to 5 Hz) stimulation of C-fibers (first order neurons) at constant intensity (Latremoliere & Woolf, 2009; Li et al., 1999). It is a process that recruits NMDA glutamate receptors (Herrero et al., 2000). Windup can be elicited by temporal summation paradigms, where increasing the frequency of repeated identical noxious stimulation will produce a heightened sensation of pain, although the intensity of the stimulation remains unchanged (Marchand, 2008). While windup can induce central sensitization, it is a transient excitability

of the spinal cord neurons that disappears quickly following the end of the stimulation as the membrane returns to its resting state, whereas central sensitization is a state that remains after the end of stimulation (Woolf, 2011). The clinical manifestations of central sensitization can be observed in hyperalgesia (amplified response to nociceptive input) and allodynia (perception of pain in the absence of nociceptive stimulation) (Marchand, 2008). Temporal summation paradigms, including paradigms employing the nociceptive-specific flexion reflex (NFR), are advantageous in an experimental setting as they allow investigating the contribution of spinal cord neurons to pain sensitization in humans (Arendt-Nielsen et al., 1994; Lévesque et al., 2012).

Finally, certain supraspinal processes were shown to increase the pain perceived. Notably, anxiety was shown to exacerbate the intensity of the pain sensation (Goffaux et al., 2011), an effect potentially mediated by the hippocampal formation (Ploghaus et al., 2001). Sad mood was also shown to increase pain unpleasantness, which was associated to a greater inferior frontal gyrus and amygdala response (Berna et al., 2010). Moreover, catastrophizing was shown to increase pain sensitivity (Kristiansen et al., 2014), which was associated with greater activity in the prefrontal and anterior cingulate cortex (Quartana et al., 2009). Therefore, these supraspinal processes appear to modulate the response of brain regions associated with affective and cognitive processes involved in pain perception.

1.2.6 Treatment

The American Chronic Pain Association (2015) identifies pharmacotherapy as the most common treatment for chronic pain. In fact, over 7 million Canadians are estimated to take pain medication (Lynch & Watson, 2006). Given the significant variability in the cause and the severity of pain (Food and Drug Administration, 2009), there are many classes of

medication with distinct mechanisms of actions available to treat the various types of pain (i.e. nociceptive, inflammatory, neuropathic, and functional). First line pharmacological treatments for nociceptive and inflammatory pain involve non-narcotics (e.g. acetaminophen) and nonsteroidal anti-inflammatory drugs. These medications target the inflammatory process at the origin of the peripheral nociceptor sensitivity (Lynch & Watson, 2006; Vane & Botting, 1998). For more severe/chronic nociceptive and inflammatory pain, opioids are recommended (World Health Organization, 1996). Opioids are, however, only employed as second line treatment for neuropathic pain because of their addictive qualities, and antidepressants and anticonvulsants are recommended instead (Attal et al., 2010; Attal et al., 2006). It is hypothesized that antidepressants exert their analgesic effect by increasing the availability of neurotransmitters that are essential to the ICPM (Portenoy & Ahmed, 2013), whereas anticonvulsants dampen spinal sensitization by reducing neuronal hyperactivity via glutamatergic and GABAergic mechanisms (Marchand, 2008; Tremont-Lukats et al., 2000). Antidepressants and anticonvulsants are prescribed to treat functional pain as well (Marchand, 2008).

Similarly to MDD, alternatives to pharmacotherapy for pain treatment include psychotherapies, somatic therapies and physical therapies (American Chronic Pain Association, 2015; Turk & Gatchel, 2002). Among psychotherapies, CBT is most commonly recommended, although mindfulness therapy as well as acceptance and commitment therapy appear as equally good alternatives for pain management (Veehof et al., 2011). Although TENS is often used to induce ICPM in research settings, the literature supporting the use of TENS in a clinical setting is still inconclusive (DeSantana et al., 2008; Nnoaham & Kumbang, 2008). Other somatic therapies in pain treatment, such as acupuncture, are employed in pain

management (American Chronic Pain Association, 2015). However, only limited research has investigated the efficacy of such treatments in pain treatment (Sun et al., 2008). Finally, physical exercise and other forms of physical therapies (e.g. yoga, tai chi, qigong) are also recommended for patients suffering from chronic pain (American Chronic Pain Association, 2015).

1.3 Comorbidity of pain and depression

1.3.1 Epidemiology

Studies show that between 50 to 65 % of patients suffering from MDD report pain symptoms (Bair et al., 2003; Katona et al., 2005), and as many as 92 % of MDD patients report at least one pain-related symptom (Corruble & Guelfi, 2000). Evidently, pain and depression co-occur frequently, and seem to be mutually exacerbating. In fact, pain in joints, limbs, back, and abdomen (Corruble & Guelfi, 2000; Garcia-Cebrian et al., 2006), as well as headaches (Mathew et al., 1981) constitute some of the common somatic symptoms that negatively impact treatment response (Bair et al., 2004), time to remission (Karp et al., 2005), daily functioning (Ohayon & Schatzberg, 2010), sleep (Ohayon, 2004), and quality of life of MDD patients (Lin et al., 2014), as well as predict disorder chronicity (Gerrits et al., 2012). Conversely, depressive symptoms were associated with poor prognosis (Bair et al., 2003), longer time to recovery (Henschke et al., 2008), higher probability of pain chronicity (Pincus et al., 2002), and poor response to treatment (Bair et al., 2003) in individuals suffering from pain.

Individuals presenting both pain and depression were found by a national survey in the U.S. to be older, with lower income, and reporting an increased use of medical services

compared to depressed individuals without comorbid pain (Bao et al., 2003), which in turn is associated with a substantial increase in medical costs (Emptage et al., 2005; Greenberg et al., 2003). Interestingly, Bao et al. (2003) also observed that depressive individuals suffering from pain were 21 % less likely to see a mental health specialist, alluding to the problem of overlapping symptomatology between MDD and certain pain conditions (Wilson et al., 2001). When presented simultaneously, patients and healthcare professionals might attribute depressive symptoms to a painful condition and vice-versa, consequently focusing on the primary condition while the secondary condition remains unattended (Katona et al., 2005; Wilson et al., 2001). Nevertheless, attending to both pain and depression when these conditions are comorbid is crucial, as they influence negatively one another.

In order to explain the frequent co-occurrence of depression and pain, certain authors have postulated that pain might be a risk factor for developing symptoms of depression, and others have suggested the opposite, that it is depression that might lead to painful symptoms. Regarding the former hypothesis, authors have posited that chronic pain might operate as a stressor activating the hypothalamic-pituitary-adrenal axis (Blackburn-Munro & Blackburn-Munro, 2001), or as a precipitating factor for a pre-existing vulnerability to develop a psychiatric disorder (Dersh et al., 2002), and therefore symptoms of depression would be the consequence of pain. General population studies have observed that pain and chronic pain might indeed precede depression (Gerrits et al., 2014; McBeth et al., 2002), and there seems to be more support for this direction of the relation between pain and depression (Fishbain et al., 1997; Goesling et al., 2013). The alternative hypothesis, where depression could bring about biological and cognitive changes that would potentially facilitate the subsequent emergence of pain (Goesling et al., 2013), has also received some attention. Painful symptoms might be the

somatization of depression, which would be a way to communicate distress (Dersh et al., 2002). In fact, a national survey has found that depression increased the risk of future chronic pain (Currie & Wang, 2005; Gupta et al., 2007).

Although the relationship between pain and depression appears to be reciprocal, only a few studies have demonstrated within the same experiment the two conditions having an equally adverse impact on one another (Goesling et al., 2013). In a population based study, pain at baseline predicted depression, and similarly depression at baseline predicted pain over 2 years (Chou, 2007). Furthermore, changes in pain severity were shown to predict subsequent depression severity over 12 month in primary care patients, as well as the converse (Kroenke et al., 2011). Overall, the relationship between pain and depression seems to be bidirectional.

1.3.2 Clinical features

Given the quantity of studies suggesting a reciprocal and bidirectional relation between depression and pain, a growing number of authors consider the frequent comorbidity between these two conditions as a result of *common* cognitive and affective factors. In fact, common cognitive factors were found to be influenced by pain and depression, and to mediate the relationship between these conditions. Specifically, deficits in working memory and attention were independently noted in pain (Moriarty & Finn, 2014; Moriarty et al., 2011) as well as in depression (Gotlib & Joormann, 2010), suggesting that individuals suffering from either conditions would have a certain difficulty to attend to stimuli that is not congruent with their condition, whereas they would display a bias towards disorder-salient stimuli (Erickson et al., 2005; Khatibi et al., 2009). Studies suggest that reduced gray matter density and altered activation of the prefrontal cortex in both conditions might be the neural substrate of this cognitive deficit (Robinson et al., 2009). The well documented implication of catastrophizing,

which is a maladaptive cognitive distortion involving processes such as rumination and magnification, in pain and depression reinforces the importance of shared cognitive processes between the two conditions (Goesling et al., 2013; Linton & Bergbom, 2011; Quartana et al., 2009). In fact, research in cognitive-behavioral interventions suggests that reduction in catastrophizing would also reflect improvements in pain severity and depression in comorbid patients (Quartana et al., 2009). Helplessness, self-efficacy, and pessimism were also shown to mediate the relationship between pain and depression (Campbell et al., 2003; Goesling et al., 2013). Negative affect, such as sadness, distress and fear have also been associated with both pain and MDD (Goesling et al., 2013). The affective component of pain is increasingly supported by results in imaging as being partially independent from the sensory component of pain. Specifically, the anterior cingulate cortex and the amygdala seem to integrate negative affect and pain (Neugebauer et al., 2004; Robinson et al., 2009; Shackman et al., 2011).

Pain processing and depression appear to share multiple neurobiological mechanisms, which could explain the frequent co-occurrence of these conditions. Serotonergic and noradrenergic signaling pathways have been implicated in the pathogenesis of MDD, and are thought to be involved in the emergence of pain when dysfunctional. The existence of common serotonergic and noradrenergic alterations in pain and depression is also suggested by the mechanism of action of pharmacological treatments common to both pain and depression (Goesling et al., 2013). Although first considered as a treatment for the affective symptoms of chronic pain, antidepressants, including SSRIs and SNRIs, are receiving increasing support as analgesics that are hypothesized to act on endogenous pain control by enhancing descending inhibitory pain mechanisms which rely on serotonin and norepinephrine (Jann & Slade, 2007; Mico et al., 2006). Still, pain management with antidepressants is most

recommended in patients presenting comorbid chronic pain and depression (Campbell et al., 2003; Goesling et al., 2013).

Alternatively, an increasing number of studies have proposed inflammatory mechanisms that could explain the link between pain and depression (Walker et al., 2014). Inflammation is pertinent in the context of pain. In fact, it is an inflammatory process that is at the origin of the sensitization of the peripheral nociceptors. In theory, a neuropathic inflammatory process might be implicated in central pain sensitization (Clark et al., 2013). Inflammatory processes might also be implicated in the pathophysiology of depression. A meta-analysis has shown interleukin-6 and C-reactive protein elevations in MDD (Haapakoski et al., 2015). Therefore, common inflammatory alterations could potentially be at the origin of the frequent co-occurrence of the two phenomena.

1.3.3 Pain perception in depression

In order to better understand the reasons underlying the elevated prevalence of painful somatic symptoms in major depression, several psychophysical studies have been performed in patients with MDD. However, current experimental studies have failed to offer a clear insight into the relationship between the two conditions (Potvin, 2011). Most studies agree that MDD patients perceive pain to be subjectively less intense than healthy individuals when administered the same intensity of pain (Boettger et al., 2010; Dworkin et al., 1995; Lopez-Sola et al., 2010). However, a number of studies have found the reverse relationship or no differences between MDD and healthy individuals (Frew & Drummond, 2009; Normand et al., 2011; Strigo et al., 2008a). Furthermore, a majority of studies investigating pain threshold found a higher pain threshold across most nociceptive stimulation modalities (e.g. thermic, electric, mechanic, and ischemic) in MDD compared to controls (Bär et al., 2007; Bar et al.,

2005; Boettger et al., 2013; Dickens et al., 2003; Schwier et al., 2010), suggesting that MDD patients might tolerate pain better than healthy individuals. Even so, substantial literature report decreased pain threshold in MDD, or no significant differences between MDD and healthy individuals (Bar et al., 2005; Klauenberg et al., 2008; Normand et al., 2011; Spernal et al., 2003; Strigo et al., 2008a; Terhaar et al., 2010). Finally, a similar pattern can be observed in studies investigating pain tolerance in MDD, with studies suggesting a higher (Bar et al., 2005; Bar et al., 2003), lower (Gormsen et al., 2004), or identical (Frew & Drummond, 2009) pain tolerance in depression. In sum, psychophysiological studies investigating pain perception found MDD patients to be hypoalgesic, hyperalgesic or normal when compared to healthy individuals (Dickens et al., 2003; Lautenbacher & Krieg, 1994; Potvin, 2011), which are overall inconsistent results that fail to determine the impact of MDD on pain perception (Dickens et al., 2003) and to explain the elevated frequency of pain complaints observed in a depressive population.

1.3.4 Pain modulation in depression

Considering that the literature investigating pain perception, pain threshold, and pain tolerance in depression is for the most part inconclusive, authors have suggested that the issue in MDD might lie in the endogenous inhibitory or excitatory pain modulation (Potvin, 2011). Taking into account that serotonin and norepinephrine were shown to be implicated in pain inhibition (Millan, 2002; Ossipov et al., 2010), as well as substantial research has identified both serotonergic and noradrenergic neural transmission abnormalities in the pathophysiology of depression (Moret & Briley, 2011; Selvaraj et al., 2011; Stockmeier, 2003), a deficit of endogenous pain inhibition in MDD seems probable. Such deficit in descending inhibitory pathways would allow for painful sensations that are normally supressed to be interpreted as

pain by the brain (Stahl & Briley, 2004), which would offer an explanation for the prevalence of painful somatic symptoms in depression. To date, few studies have investigated descending pain inhibition, with inconsistent results. Measuring the jaw-opening reflex, Wang et al. (2000) observed no deficit in inhibitory mechanisms, whereas Bar et al. (2003) found better pain inhibition in MDD than in controls. However, the association between the jaw-opening reflex and pain processing has been questioned by certain authors (Forkmann et al., 2009). In a recent study from our group, Normand et al. (2011) set out to measure deficits in pain inhibition in individuals suffering from MDD using an experimental thermal pain paradigm. Participants were administered two temporal summation tests using heat pulses, and a cold pressor test was conducted in between to induce inhibitory conditioned pain modulation. Remarkably, our group found no deficits in pain inhibition in MDD patients (Normand et al., 2011).

Although very little literature has addressed the alternative hypothesis, painful somatic symptoms in MDD might emerge from overactive excitatory pain mechanisms. Endogenous excitatory pain mechanisms were found to be mediated by glutamatergic mechanisms (Gebhart, 2004; Herrero et al., 2000; Porreca et al., 2002; Woolf, 2004), and they are most frequently studied using temporal summation paradigms (Potvin et al., 2012; Potvin et al., 2008). Notably, recent studies suggest an implication of glutamatergic disturbances in the pathophysiology of depression (Hashimoto, 2009; Mitchell & Baker, 2010; Sanacora et al., 2008), which might result in a potential disruption of endogenous excitatory pain mechanisms in MDD. To date, Klauenberg et al. (2008) are the only group to have assessed endogenous excitatory mechanisms in depression. Using a mechanical temporal summation paradigm, the authors observed an increase in pain sensitization in depressive disorders and found no

differences in pain threshold between depressive participants and controls (Klauenberg et al., 2008). These results might indicate overactive excitatory pain mechanisms in depression. However, the sample recruited by Klauenberg et al. (2008) also included patients suffering from mood disorders other than MDD, such as bipolar disorder, adjustment disorder and dysthymia, thereby limiting the generalizability of the results. Moreover, the paradigm employed to induce temporal summation did not allow the separation of the spinal and supraspinal aspects of pain sensitization in depression.

1.3.5 Treatment

There are currently no set guidelines available for the treatment of unexplained painful somatic symptoms in patients with MDD, and there are only few suggestions for the treatment of comorbid pain and MDD. The National Institute of Mental Health (2015) proposes SSRIs and SNRs as pharmacotherapies, and CBT as psychotherapy for the treatment of chronic pain and depression. Similarly, Nicolson (2010) suggests antidepressants (SNRIs and TCAs), as it appears to relieve neuropathic pain. However, these are circumstantial evidences that do not indicate whether the aforementioned treatments are optimal in MDD patients presenting unexplained somatic symptoms.

1.4 Objectives

The neurobiological mechanisms underlying the high prevalence of painful somatic symptoms in major depression are yet to be fully understood. Considering that studies investigating pain perception in MDD have yielded inconsistent results, recent studies have focused on characterizing endogenous inhibitory and excitatory pain mechanisms in MDD. Normand et al. (2011) found no deficits in endogenous inhibitory pain modulation in MDD. Conversely, Klauenberg et al. (2008) showed that pain sensitization might be disrupted in patients with mood-disorder, which is an indication of potentially altered excitatory pain mechanisms. However, no studies to date have investigated simultaneously the contribution of spinal and supraspinal processes in pain sensitization in MDD.

The primary purpose of this study was to investigate excitatory pain mechanisms in major depression. We set out to replicate the increased pain sensitization observed by Klauenberg et al. (2008) in MDD patients exclusively. In order to study endogenous excitatory pain mechanisms, we employed a temporal summation paradigm that enabled us to assess the contribution of spinal and supraspinal processes in pain sensitization in MDD. To this effect, we measured the NFR triggered by a transcutaneous electrical stimulation to assess the contribution of spinal processes to pain sensitization. Furthermore, by measuring the subjective pain during the temporal summation paradigm, we assessed the contribution of supraspinal processes to pain sensitization. Therefore, our second objective was to evaluate whether the alteration of pain sensitization in MDD has spinal and/or supraspinal origins. Given the substantial literature addressing the subject of supraspinal disturbances in depression, we hypothesize that MDD patients will demonstrate an altered supraspinal pain

sensitization. Finally, we set out to assess the clinical correlates of the experimentally-induced pain response.

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Valérie Tourjman was involved in patient recruitment and assessment, as well as revision of the manuscript.

Philippe Chalaye was involved in participant testing and provided critical comments about the manuscript.

Serge Marchand was involved in study design and provided critical comments about the manuscript.

Stéphane Potvin was involved in study design, supervised Andràs Tikàsz, and was involved in the revision of the manuscript

All authors have revised and approved the final version of the article.

Increased spinal pain sensitization: A new explanation

for highly prevalent painful somatic symptoms in major depressive disorder?

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Abstract

Objectives. Although patients suffering from major depressive disorder (MDD) often complain from painful symptoms, the relationship between pain and depression has yet to be clearly characterized. Only recently have studies employing temporal summation paradigms offered some preliminary insight into the co-occurrence of pain and depression. This study sets out to evaluate the contribution of spinal and supraspinal processes in pain sensitization in MDD using a temporal summation paradigm.

Subjects. Thirteen healthy controls and fourteen MDD patients were included in the final analysis. Diagnosis was made according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV-TR.

Methods. To induce temporal summation, we used low- and high-frequency intermittent stimulations of the sural nerve, as previously employed by our laboratory. Spinal pain sensitization was quantified by measuring the change in the amplitude of the nociceptive-specific flexion reflex (NFR) response, and supraspinal pain sensitization was obtained by measuring change in subjective pain rating, from the low- to high-frequency stimulation condition.

Results. We found an increased sensitization in the NFR response in MDD patients in the high-frequency condition, which did not translate into an increased amplification of their subjective responses during testing. However, we found a positive association between spinal sensitization and painful somatic symptoms in MDD patients.

Conclusion. Together, these results suggest increased spinal pain sensitization in MDD, which might explain the high prevalence of painful somatic symptoms in these patients.

Key words: Major depressive disorder – pain – nociceptive reflex – sensitization

Introduction

Pain and depression often co-occur, with an estimated 65 % of patients suffering from major depressive disorder (MDD) reporting pain symptoms [1], and as many as 92 % of MDD patients reporting at least one pain-related symptom [2]. Pain in joints, limbs, back, and abdomen [2, 3], as well as headaches [4] constitute some of the common somatic symptoms that negatively impact treatment response [5], time to remission [6], daily functioning and quality of life of MDD patients [7].

Despite the high prevalence and negative consequences of these symptoms, current experimental studies have failed to offer a clear insight into the relationship between pain and depression [8]. Psychophysiological studies investigating pain thresholds found MDD patients to be hypoalgesic, hyperalgesic or normal when compared to healthy individuals [8-10]. These inconsistent results hardly account for the reported frequency of pain complaints in MDD. As an alternative explanation, authors have suggested that the issue in MDD might lie in the endogenous inhibitory or excitatory modulation of pain and not with pain perception [8]. Considering that serotonin and norepinephrine have been associated with pain inhibition [11, 12], as well as substantial research has identified both monoamines as crucial in depression [13, 14], a deficit in endogenous pain inhibition in MDD seems plausible. However, our group found no deficits in pain inhibition in MDD patients [15]. Although a largely unexplored hypothesis, painful somatic symptoms in MDD might arise from overactive excitatory pain mechanisms. Pain facilitation is usually studied using temporal summation paradigms [16], and is known to be dependent on glutamatergic mechanisms [17, 18]. Interestingly, recent evidence suggests that glutamatergic disturbances play a key role in the pathophysiology of MDD [19, 20], hinting at a possible disruption of endogenous excitatory pain mechanisms in

MDD. To date, the only study to assess endogenous excitatory mechanisms in depression found an increase in pain sensitization, as measured with a mechanical temporal summation paradigm [21]. Unfortunately, the depressive sample investigated included patients with bipolar disorder, adjustment disorder and dysthymia, which limits the generalizability of the results. Furthermore, the paradigm used to induce temporal summation did not allow the separation of the spinal and supraspinal aspects of pain sensitization in depression.

In order to study the contribution of spinal cord neurons to pain sensitization in humans, past studies from our group and others have relied on the transcutaneous electrical pain paradigm [22, 23]. This paradigm relies on the stimulation of the sural nerve, which triggers a nociceptive-specific flexion reflex (NFR) response. Studies have shown that rapid stimulation of the sural nerve induces an increase of the NFR amplitude and of the subjective pain in humans [22]. Therefore, this paradigm can be used to investigate the contribution of spinal processes to pain sensitization [24]. Employing the above-mentioned paradigm [23] using both low- and high-frequency intermittent stimulations of the sural nerve in a MDD population along with a measure of subjective pain would allow quantifying the contribution of spinal and supraspinal processes in pain sensitization.

The purpose of this study was to evaluate the contribution of spinal and supraspinal processes in pain sensitization in MDD. This study set out to: 1) replicate the increased pain sensitization observed by Klauenberg et al. [21] in a sample of MDD patients exclusively; 2) assess the spinal and supraspinal aspects of pain sensitization in MDD patients; and 3) correlate experimentally-induced pain responses with clinical symptoms.

Methods

Participants

MDD patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV-TR by a psychiatrist (VT). Both groups of participants (healthy or depressive) were not eligible to participate if they were diabetic, underage (under 18 years old), suffering from a medical condition associated with chronic pain, or used analgesics (last 24 hours), anabolic steroids or androgens. After carefully explaining the objectives and experimental procedures of the study, free and informed consent was obtained from all participants. The study was approved by local ethics committees.

Of a total of 17 MDD subjects who participated in the study, 14 MDD patients were retained for the final analysis (see Table 1). One participant was excluded because he/she was diagnosed with bipolar disorder, one participant was diabetic, and one participant had taken analgesic medication prior to testing. All 13 healthy controls recruited were retained for the final analysis. Patients and controls did not differ in terms of age, gender, ethnicity, marital status, education level, smoking status, weight and body mass index (Table 1). At the time of testing, MDD participants were treated with one or more drugs from the following: selective serotonin reuptake inhibitors (n=6), serotonin-norepinephrine reuptake inhibitors (n=7), norepinephrine-dopamine reuptake inhibitors (n=3), tricyclic antidepressants (n=1), other antidepressants (n=4) and second-generation antipsychotics (n=5). Healthy controls were not under any medications for psychiatric conditions.

Measures

Symptom Evaluation

All participants completed self-reported questionnaires first. The Beck Depression Inventory (BDI) was used to assess the severity of depression [25]. The State-Trait Anxiety Inventory (STAI) was used to assess state anxiety (STAI-Y1) and trait anxiety (STAI-Y2) [26]. Visual analogue scales (VAS) were used to assess (over the last 7 days) clinical pain, migraines, pain in back, shoulders, abdomen, stomach, articulations, how much pain affects the completion of daily tasks, as well as pain level during the day in MDD patients [27]. Following the completion of the questionnaires, participants were fitted with electromyographic (EMG) electrodes. Pain and withdrawal reflex thresholds were subsequently measured.

Sural Nerve Stimulations

Painful stimulations were administered through non-invasive transcutaneous electrical stimulations of the sural nerve (across the retromalleolar path of the left leg), as described by Goffaux et al. [28]. When stimulation currents are strong enough to recruit A-δ fibers, a NFR response is triggered, whose amplitude correlates positively with subjective pain [29]. Importantly, studies have shown that the rapid stimulation of the sural nerve (i.e. 0.3 Hz or faster) induces a temporary hyper-excitability of spinal cord neurons in animals [30, 31], which is observed as an increase of the NFR amplitude in humans, as well as an increase in subjective pain [22]. In the current study, a stimulation consisted of a volley of five electrical pulses (square waves, each 1 millisecond long) administered at a rate of 240 Hz using a constant current stimulator. A stimulation volley lasted 21 milliseconds (according to Goffaux et al. [28]). Stimulations produced an NFR response that was measured via an EMG recording

of the biceps femoris (i.e. knee-flexor muscle). Reflex threshold was determined using an iterative staircase method [32]. EMG activity was considered reflexive when the amplitude exceeded baseline activity levels by at least 1.5 standard deviations. Withdrawal reflex activity was quantified by calculating the integral of the rectified EMG signal between 90 and 150 milliseconds. EMG activity was cleaned by filtering raw EMG activity with a low-pass filter of 0.5 Hz and a high-pass filter of 100 Hz. Corrected baseline EMG activity between -100 and 0ms was used for every stimulation to determine reflex activity while controlling for potential carry-over effects (i.e. changes in baseline EMG activity).

Experimental Protocol

Participants were comfortably seated in a semi-reclined position. Testing consisted of a series stimulations administered repeatedly to the sural nerve for 4 minutes (240 seconds). Stimulation intensity was set at 15 % above the reflex threshold and remained constant throughout testing. During the first 3 minutes, sural nerve stimulation volleys were provided at a fixed frequency of 0.14 Hz (i.e. once every 7 seconds). During the last 60 seconds, stimulation frequency increased to 1 Hz (i.e. once every second). The first 3 minutes of testing represent the low-frequency condition and the last 20 seconds of testing represent the high-frequency condition. Consistent with previous research focusing on the interaction between stimulation frequency and pain, change (%) in response (subjective pain and reflex amplitude) from the low- to high- frequency condition was used as our metric of spinal pain sensitization [22]. Our analyses were based on the response to all 26 stimuli delivered at 0.14 Hz and to the first 20 stimuli at 1 Hz. Overall, 0.6 % of the trials (1 trial in the MDD group, 3 trials in the control group) were eliminated for the 0.14 Hz condition and 6.3 % of the trials (23 trials in

the MDD group, 11 trials in the control group) for the 1 Hz condition. A verbal numerical rating scale, ranging from 0 (no pain) to 100 (pain tolerance), was used to evaluate the intensity of pain during testing. Verbal pain intensity ratings were obtained every 30 seconds during the low-frequency condition and every 10 seconds during the high-frequency condition. Participants were asked to rate the intensity of the last shock received.

Data Analysis

Between-group differences were assessed using analyses of variance (ANOVAs). The dependent variables investigated were self-reported questionnaires (BDI, STAI, VAS), pain thresholds (subjective, NFR), pain perception (0.14 Hz condition; subjective, NFR) and spinal pain sensitization (1 Hz condition; subjective, NFR). Pearson's correlations were performed between clinical and pain measures. Finally, analyses of covariance (ANCOVAs) were performed to determine the potential influence of clinical variables on between-group differences in experimental pain measures. The Kolmogorov-Smirnov one-sample test indicated that all variables were normally distributed ($p>0.05$). For all analyses, statistical threshold was set at $\alpha<0.05$.

The nociceptive reflex is a robust neurophysiologic procedure, and studies using this paradigm regularly detect large effects [23, 28, 54]. Using a Cohen's d of 1.0, we calculated that 34 participants (divided in 2 groups of 17 subjects) would be required to detect a significant difference (alpha=0.05) in spinal pain sensitization between MDD patients and controls with a statistical power higher than 80 %.

Results

Self-report questionnaires

MDD patients scored significantly higher than healthy controls on all questionnaires (Table 2). MDD patients reported clinically significant symptoms for both depression and anxiety. Using a VAS cut-off of >30 to indicate moderate pain [33, 34], we found that 4 MDD patients reported one or more of the following painful somatic symptoms: pain in the stomach (n=2), back pain (n=3), shoulder pain (n=1), pain in the articulations (n=2) and migraine (n=4).

Pain thresholds

There was no significant difference in pain threshold and withdrawal reflex threshold between MDD patients and healthy controls (Table 3).

Pain perception (0.14 Hz condition)

There was no significant difference between MDD patients and healthy controls in the low-frequency condition in subjective pain rating and the amplitude of NFR response (Table 3).

Pain sensitization (1 Hz condition)

There was no significant difference in the subjective pain rating between MDD patients and healthy controls in the high-frequency condition. Similarly, there was no significant difference in the increase of the subjective pain rating from low- to high- frequency stimulation between the two groups (Table 3). However, MDD patients showed significantly higher NFR response amplitudes than healthy controls, as shown in Figure 1, in the high-frequency condition. The magnitude of the difference in spinal pain sensitization was large (Cohen's d = 0.88). The

difference in the sensitization of the NFR response amplitude, measured by the % augmentation from low- to high- frequency stimulation condition, was also significant between the two groups (Table 3).

Correlation analyses

Across groups, we found a significant positive correlation between state anxiety (STAI-Y1) and the augmentation in NFR amplitude from low- to high-frequency stimulation, as well as the amplitude of the NFR in the high-frequency condition. In the MDD group, the average VAS pain score significantly correlated with the augmentation in NFR amplitude from low- to high- frequency stimulation. No other significant correlation was found between clinical variables and experimental pain measures (Table 4). Between-group differences in spinal sensitization remained significant after adjusting for anxiety in the ANCOVA ($p< 0.05$).

Discussion

In this study, we set out to evaluate the contribution of spinal and supraspinal processes in pain sensitization in MDD using a temporal summation paradigm. Similarly to Klauenberg et al. [21], we observed an increase in spinal pain sensitization in MDD patients compared to healthy controls, whereas pain thresholds and pain perception were relatively normal. More precisely, we found an increased sensitization in the NFR response in MDD patients in the high-frequency condition, which did not translate into an increased amplification of their subjective responses. Painful somatic symptoms in MDD were associated with the increase in NFR amplitude from low- to high- frequency stimulation across groups. Lastly, state anxiety

was associated with the increase in NFR amplitude from low- to high- frequency stimulation across groups.

Our results are indicative of altered spinal sensitization, and not pain perception, in MDD. Previous studies assessing pain threshold have observed increased [35], decreased [36], as well as normal [37] thresholds in MDD, regardless of the pain modality assessed [8]. Therefore, the observed lack of difference in pain threshold between MDD and healthy subjects is not at odds with the current state of the literature. Moreover, a recent study assessing NFR response in MDD patients found no difference in NFR thresholds between MDD and healthy subjects [38], a result consistent with our own findings. Taken together, these results suggest that pain perception is relatively normal in MDD. More importantly, we observed an increased spinal pain sensitization in MDD, which is consistent with results previously observed in a group of patients with mood disorders in a study employing a mechanical temporal summation paradigm [21]. Considering that endogenous inhibitory pain mechanisms seem to be normal in MDD, as shown by Normand et al. [15], these results suggest that excitatory pain mechanisms might be overactive in MDD.

Overactive excitatory pain mechanisms in MDD might in turn offer an explanation for the high prevalence of painful somatic symptoms in these patients. Growing evidence suggests that central pain sensitization is not only a core feature of neuropathic pain, but is also involved in other chronic pain conditions, such as fibromyalgia, osteoarthritis, headache, and temporomandibular joint disorder [39]. Furthermore, greater temporal summation prior to a painful surgery in a pain-free healthy population predicted higher postoperative pain scores [40], suggesting that central sensitization might play a role in the transition from acute to chronic pain [41]. The increased temporal summation observed in MDD patients might then

be interpreted as a sign of vulnerability of MDD individuals to develop chronic pain. Indeed, despite the relatively low levels of somatic pain symptoms reported by MDD patients in the current study, we found a significant relationship between spinal pain sensitization and self-reported painful somatic symptoms in MDD patients.

The results of the current study suggest that the spinal component of pain sensitization, and not the supraspinal component, is abnormal in MDD patients. This result might seem surprising at first glance, since abnormalities in prefrontal and limbic brain regions, as well as in the emotion-pain circuitry have been consistently identified in MDD [42-44]. Increased "emotional allodynia" have also been reported in depression [45]. Therefore, a supraspinal origin for the pain sensitization in MDD might have been expected. Instead, our results indicate that the relay of nociceptive input to the central nervous system is already amplified at the spinal level, which is a novel observation. To our knowledge, this mechanism has not been previously studied in this population. As for the absence of supraspinal pain sensitization, it might be attributable to the fact that our sample did not include patients suffering from chronic pain and/or to the analgesic effect of antidepressants [46]. In keeping with this idea, Terry et al. [38] observed a disrupted emotional pain modulation in a drug-free MDD sample, a result that was not replicated in medicated MDD patients [47]. Potentially, we might have observed supraspinal pain sensitization in MDD patients had we investigated emotional modulation. However, it should be noted that Terry et al. [38] were interested in the emotional modulation of spinal pain sensitivity, not the emotion modulation of spinal pain sensitization. Although the amplification of subjective pain during the high-frequency condition was not increased in MDD patients, relative to controls, the increased spinal pain sensitization observed in patients was correlated with supraspinal factors, as there was a significant association with state

anxiety. Consistent with previous reports of an association between anxiety and temporal summation of pain [48], this result may reflect pain anticipation effects, which have been demonstrated in MDD patients previously [36, 49].

Our results seem to agree with emerging neurobiological models of MDD. Studies have found pain facilitation, a process usually assessed via temporal summation paradigms [16], to be associated with glutamatergic mechanisms [17, 18]. Temporal summation of pain is thought to reflect the progressive enhancement of C-fiber evoked responses of dorsal horn neurons (windup) and seems to be dependent on N-methyl-D-aspartate (NMDA) glutamate receptor mechanisms in both animals [50] and humans [51]. Interestingly, increased levels of glutamate in the brain [52] and altered expression of glutamate-related genes were recently observed in depressive patients [53], suggesting that glutamatergic disturbances might play a role in the pathophysiology of MDD [19, 20]. Along those lines, preliminary studies found the NMDA receptor antagonist ketamine, an analgesic, to exert beneficial therapeutic effect in MDD patients [54-56]. Although neurotransmitters were not measured in the current study, the results reported here suggest that the increased spinal pain sensitization observed in MDD might result from glutamatergic mechanisms. This hypothesis will need to be further explored in future experiments.

The current study has a few limitations. First, we acknowledge that the small sample size of this study limits the generalizability of the results. It is however noteworthy that the effect size observed for the difference in spinal sensitization between MDD patients and healthy controls was large. The NFR is a robust neurophysiologic phenomenon, and studies employing this procedure typically involve small samples [23, 28, 38, 57]. Nevertheless, future studies should seek to replicate the increased spinal pain sensitization observed in MDD

patients in larger samples, in order to reduce the risk of sampling bias. The medication of MDD patients at the time of the experiment might also be a concern. Antidepressants have well-known analgesic properties [46], which might explain the failure of the current study to observe decreased pain thresholds, increased pain perception (in the low-frequency condition), as well as increased supraspinal pain sensitization in MDD patients. However, medication does not explain our main results as, despite the analgesic properties of antidepressant medication, we still observed an increased spinal pain sensitization in MDD. Finally, the study followed a cross-sectional design. Therefore, it is difficult to assess whether heightened spinal pain sensitization in MDD is a risk factor for chronic pain or not. In the future, it would be relevant to examine the association between temporal summation of pain and pain symptoms longitudinally, starting with MDD subjects showing little or no painful somatic symptoms at baseline.

To our knowledge, the current study shows for the first time that spinal pain sensitization is altered in MDD, and that the modulation of nociceptive input is already amplified at the spinal level. Future studies should replicate this finding in large samples of drug-free MDD patients, and will need to determine whether this neurophysiological model predicts the emergence of painful somatic symptoms in this population.

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Figure 1 Mean nociceptive-specific flexion reflex amplitude obtained at low- (0.14 Hz) and high- (1 Hz) frequency stimulation for MDD patients and healthy controls. All 26 stimulations in the 0.14 Hz stimulation condition and all 20 stimulation in the 1 Hz stimulation condition are shown.

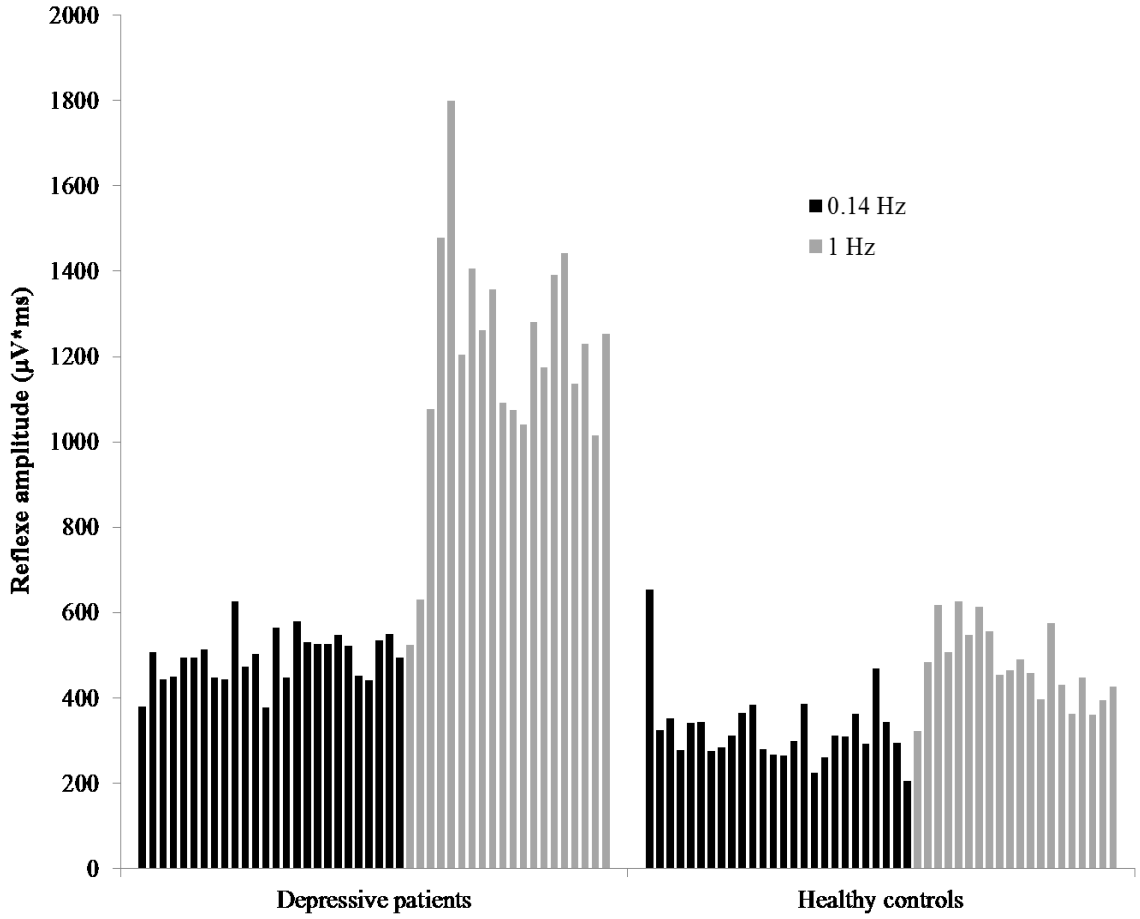

Table 1 Demographic characteristics of participants, given as mean ± standard error.

	MDD (n = 14)	HC (n = 13)	Statistics	Cohen's d
Age	41.71 ± 3.22	42.85 ± 3.92	t= -0.225, p= 0.824	0.08
Gender (Female)	10	9	χ^2= 0.016, p= 0.901	0.06
Ethnicity (Caucasian)	11	11	χ^2= 1.333, p= 0.513	0.22
Marital status (Single)	7	3	χ^2= 1.710, p= 0.425	0.66
Smoker	5	2	χ^2= 1.192, p= 0.275	0.62
Education (Years)	13.71 ± 0.412	14.62 ± 0.417	t= -1.537, p= 0.137	0.61
Weight (kg)	73.63 ± 3.83	68.03 ± 4.40	t= 0.963, p= 0.345	0.37
Body Mass Index	25.90 ± 1.11	24.85 ± 1.12	t= 0.666, p= 0.512	0.26

HC: healthy, psychopathology-free control participants; MDD: participants with major depressive disorder.

Table 2 Mean (± standard error) response to self-report questionnaires.

	MDD (n = 14)	HC (n = 13)	Statistics	Cohen's d
STAI-Y1	46.50 ± 2.79	27.85 ± 2.38	F = 25.526, p< *0.001*	1.94
STAI-Y2	54.14 ± 1.82	33.46 ± 2.03	F = 58.083, p< *0.001*	2.93
BDI	19.36 ± 1.72	3.23 ± 0.75	F = 69.616, p< *0.001*	3.22
VAS (Average)	26.30 ± 5.24	...	…	…

BDI: Beck Depression Inventory; HC: healthy, psychopathology-free control participants; STAI-Y1: State Anxiety Inventory; STAI-Y2: Trait Anxiety Inventory; MDD: participants with major depressive disorder; VAS: Visual Analogue Scales. Note: the VAS score reported is the average of all nine VAS participants filled out regarding pain symptoms they experienced in the last seven days.

Table 3 Thresholds, NFR response and subjective pain rating, given as mean ± standard error.

	MDD (n = 14)	HC (n = 13)	Statistics	Cohen's d
Threshold				
Pain (mA)	9.11 ± 0.96	8.32 ± 1.78	F= 0.159, p= 0.693	0.15
Reflex (mA)	14.90 ± 1.99	12.44 ± 1.79	F= 0.841, p= 0.368	0.35
Low-frequency (0.14 Hz)				
Pain rating	38.08 ± 5.89	26.32 ± 5.19	F= 2.215, p= 0.149	0.57
NFR (µV *ms)	493.79 ± 77.38	333.32 ± 66.62	F= 2.464, p= 0.129	0.61
High-frequency (1 Hz)				
Pain rating	56.25 ± 7.78	40.07 ± 6.54	F= 2.493, p= 0.127	0.61
NFR (µV *ms)	1139.26 ± 249.00	496.53 ± 116.01	F= 5.201, *p= 0.031*	0.88
Sensitization				
Pain rating (% augmentation)	146.42 ± 10.91	168.86 ± 22.94	F= 0.818, p= 0.374	0.34
NFR (% augmentation)	234.60 ± 31.36	152.47 ± 20.20	F= 4.685, *p= 0.040*	0.83

HC: healthy, psychopathology-free control participants; MDD: participants with major depressive disorder

Table 4 Correlations between clinical and experimental measures across groups.

	STAI-Y1	STAI-Y2	BDI
Threshold			
Pain (mA)	r=0.012, p=0.951	r=-0.011, p=0.955	r=0.047, p=0.814
Reflex (mA)	r=0.024, p=0.906	r=0.004, p=0.986	r=-0.012, p=0.953
Low-frequency (0.14 Hz)			
Pain rating	r=0.089, p=0.661	r=0.095, p=0.638	r=0.080, p=0.692
NFR (μV *ms)	r=0.302, p=0.126	r=0.336, p=0.087	r=0.232, p=0.244
High-frequency (1 Hz)			
Pain rating	r=0.131, p=0.515	r=0.113, p=0.575	r=0.133, p=0.508
NFR (μV *ms)	r=0.429, p=***0.026***	r=0.338, p=0.085	r=0.298, p=0.132
Sensitization			
Pain rating (% augmentation)	r=-0.115, p=0.568	r=-0.198, p=0.322	r=-0.116, p=0.566
NFR (% augmentation)	r=0.468, p=***0.014***	r=0.205, p=0.305	r=0.257, p=0.196

BDI: Beck Depression Inventory; STAI-Y1: State Anxiety Inventory; STAI-Y2: Trait Anxiety Inventory

3 Discussion

The aim of this study was to evaluate the contribution of spinal and supraspinal processes to pain sensitization in MDD. For this purpose, we employed a temporal summation paradigm to induce pain sensitization while measuring subjective pain perception and the amplitude of the NFR response. We observed an increased sensitization of the NFR amplitude in MDD patients compared to healthy controls, which suggests that spinal pain sensitization is altered in MDD. Conversely, we did not observe an increased sensitization of subjective pain ratings in MDD, suggesting that supraspinal pain processes remain unaltered in MDD. Furthermore, there were no between-group differences in pain threshold and in NFR threshold.

3.1 Pain threshold and NFR threshold

In the present study, we did not detect a difference in subjective pain threshold and NFR threshold between MDD patients and healthy controls, indicating that pain perception as well as nociception might not be affected in MDD. As mentioned earlier, the literature regarding pain threshold in MDD, independently of the pain modality assessed, is quite inconsistent (Potvin, 2011). Studies have reported increased (Bär et al., 2007), decreased (Strigo et al., 2008b), and even normal (Lautenbacher et al., 1999) pain thresholds in MDD patients, rendering the characterization of pain sensitivity especially difficult in this disorder. Neziri et al. (2010) reported that lower pain threshold was associated with higher depressive scores on the Beck Depression Inventory, yet the NFR threshold was not associated with depression. Furthermore, Terry et al. (2013) did not observe a difference in NFR threshold between MDD patients and healthy controls, which is consistent with our results in suggesting that spinal nociceptive processing is normal in MDD. Overall, the lack of difference in experimental pain

and NFR thresholds between MDD patients and healthy subjects in our study do not seem to oppose the current state of the literature.

3.2 Spinal pain sensitization

With previous studies observing intact ICPM in MDD patients (Normand et al., 2011) and increased temporal summation of pain in mood-disorder patients (Klauenberg et al., 2008), indicating respectively normal endogenous inhibitory mechanisms and potentially disrupted endogenous excitatory mechanisms in depression, our results showing increased spinal pain sensitization in MDD might potentially imply that excitatory pain mechanisms are overactive in MDD. Considering that the paradigm employed by Klauenberg et al. (2008) did not allow the separation of spinal and supraspinal aspects of pain sensitization, this is the first study, to our knowledge, to suggest that spinal pain sensitization is altered in MDD, and that the modulation of nociceptive input is already amplified at the spinal level.

A growing number of experimental studies have found that central pain sensitization is characteristic of chronic pain conditions such as fibromyalgia, osteoarthritis, headache, knee pain, whiplash, and temporomandibular joint disorder (Lim et al., 2011; Woolf, 2011). In fact, the temporal summation of the NFR is one of the paradigms previously applied to investigate central sensitization in chronic pain conditions such as chronic whiplash pain and fibromyalgia (Banic et al., 2004). Recently, studies have reported that central sensitization can be evoked in pain-free individuals and measured for up to a week following a minor routine painful surgery (Juhl et al., 2008), and that a susceptibility toward greater temporal summation prior to a painful surgery in pain-free individuals could predict higher postoperative pain scores (Weissman-Fogel et al., 2009). These results suggest that central sensitization might play a role in the transition from acute to chronic pain (Juhl et al., 2008). At the moment of

administering the pain paradigm, the MDD patients included in the current study reported low levels of painful somatic symptoms. However, these self-reported somatic symptoms were significantly associated with the sensitization of the NFR in MDD. In light of these findings, the increased temporal summation we observed in MDD patients could be interpreted as a susceptibility to develop chronic pain in the event of a painful incident or injury. This possible vulnerability of MDD patients, which we observed as overactive excitatory pain mechanisms, might provide an explanation for the high prevalence of painful somatic symptoms in depression.

It is noteworthy that we have observed a difference in NFR sensitization between MDD patients and healthy controls, even though NFR thresholds in MDD did not differ from those of healthy controls. Given that both are measures of spinal pain processes, similar results might have been expected. For example, both disrupted NFR threshold and NFR sensitization were found in certain central pain disorders (Banic et al., 2004). Conversely, normal NFR threshold and NFR sensitization were reported in schizophrenia patients (Lévesque et al., 2012). It is however possible for these measures to lack concordance, and such results are plausible considering that the NFR, a physiological measure of spinal nociception (Terry et al., 2013), and the temporal summation of NFR, a measure of the contribution of spinal cord neurons to pain sensitization (Lévesque et al., 2012), recruit distinct yet overlapping pathways. The NFR is elicited by both Aδ-fibers and C-fibers. Due to the slow conduction of C-fibers, an increase in the frequency of noxious stimulations will result in augmented discharge of secondary spino-thalamic neurons. Whereas NFR thresholds are mediated by both Aδ-fibers and C-fibers, temporal summation of NFR is mainly mediated by C-fibers (Kimura & Kontani, 2008), thereby explaining these seemingly contradicting results.

3.3 Supraspinal pain sensitization

We did not observe a disrupted *subjective* pain sensitization in MDD patients when compared to healthy individuals, which suggests that the supraspinal component of pain sensitization is normal in MDD patients. Considering the substantial literature addressing the subject of supraspinal disturbances in depression, these results might be somewhat unexpected. Abnormal neural activity has been documented in frontal and prefrontal regions (Hamilton et al., 2012), in limbic brain regions (Drevets, 2000), and in the hippocampus (Milne et al., 2012) in depression. Furthermore, Savitz and Drevets (2009) found a disrupted fronto-limbic connectivity in MDD. Experimental pain studies employing neuroimaging have also shown abnormalities in the emotion-pain circuitry (Graff-Guerrero et al., 2008) and the cognition-pain circuitry (Bär et al., 2007) of MDD patients. These studies argue that a supraspinal origin for the pain sensitization observed by Klauenberg et al. (2008) in depressive patients might have been more probable.

Recent studies show that we could have potentially measured altered supraspinal pain processes in MDD, had we investigated supraspinal sensitization differently. Terry et al. (2013) observed a disrupted emotional pain modulation and intact spinal nociception in a MDD sample. Unlike healthy individuals, MDD patients did not modulate their subjective pain response according to the emotional videos that were shown, an effect that appears to be specific to non-medicated MDD patients (Rhudy et al., 2012; Terhaar et al., 2010). Despite the fact that these studies investigated spinal pain sensitivity, these results indicate that simply looking at subjective pain ratings might not be enough to measure the effect of disrupted supraspinal pain mechanisms.

Of further concern is the potential contribution of the depressive symptoms reported by the MDD patients recruited in this study on their pain ratings. Specifically, the average score of MDD patients on the BDI is moderate, suggesting that the MDD patients did not experience severe symptoms of depression at the time of the study. Given the increasing data showing a bidirectional relationship between pain and depression (Chou, 2007; Goesling et al., 2013 Kroenke et al., 2011), low levels of subjective depressive symptoms could influence the evaluation of the subjective pain felt by the MDD patients during the pain paradigm. Consequently, disrupted supraspinal pain mechanisms might have been observed in a sample of MDD patients evaluating their symptoms of depression as more severe.

3.3.1 Pain sensitization and anxiety

Although we did not measure an altered sensitization of the subjective pain in MDD participants relative to healthy controls during the pain paradigm, spinal pain sensitization was associated with anxiety across groups. This indicates that supraspinal factors might in fact have an influence on the effect we observed. Previous studies have reported an association between pain sensitization and anxiety (Granot et al., 2006; Robinson et al., 2010; Robinson et al., 2004), which is consistent with our results. However, Rhudy et al. (2011) found pain anxiety, and Terry et al. (2012) found anxiety sensitivity to be associated with the sensitization of subjective pain, and not spinal pain sensitization as measured by the temporal summation of the NFR. It is important to note that between-group differences in spinal sensitization remained significant after adjusting for anxiety in our study, as well as we observed an association between painful somatic symptoms and increased spinal pain sensitization in MDD patients. Together, these results indicate that the increased spinal pain sensitization we observed in MDD is not the consequence of the participants' anxiety. Hypothetically, the

association between anxiety and increased spinal sensitization in MDD patients may reflect anticipation effects. Interestingly, a recent fMRI study showed that MDD patients had increased activations, during pain anticipation of high intensity noxious thermal stimuli, in key regions of the pain matrix (e.g. anterior insula), despite ratings of pain intensity and unpleasantness similar to those of healthy controls (Strigo et al., 2013).

3.4 Limitations

Even though we find our results to be promising, there are a few factors limiting the generalizability of our observations that need to be considered. These limitations will have to be addressed in future studies.

3.4.1 Sample size

One of the main limitations of this study is the small size of the sample recruited for the experiment. In total, we included 14 MDD patients and 13 healthy individuals in our analysis, and found a significant difference in NFR sensitization and no difference in subjective pain sensitization between the two groups. However, given the restricted size of the groups, we cannot rule out a sampling bias. As a matter of fact, relatively few MDD patients in our study reported painful somatic symptoms, whereas broad cohort studies have found those symptoms to be more prevalent in MDD (Bair et al., 2003). The depressive individuals in our study could be less prone to report pain, which might explain why we did not measure a significantly increased subjective pain sensitization in MDD patients. Nevertheless, MDD patients suffering from medical conditions associated with chronic pain were not eligible to participate in our study. Given that MDD patients presenting chronic pain are usually factored in these cohort studies (Bair et al., 2003), we cannot assume that MDD patients participating in our study

were less expressive of their pain. Similarly, the increased spinal pain sensitization we observed could be specific to this particular sample. However, most studies employing a pain paradigm where the outcome is measured by the temporal summation of the NFR have successfully investigated central sensitization in groups of less than 16 participants (Terry et al., 2011). The nociceptive reflex is a robust neurophysiologic procedure, and studies using this paradigm regularly detect large effects (Guirimand et al., 2000; Lévesque et al., 2012; Lim et al., 2011; Terry et al., 2013). Furthermore, a study done in patients diagnosed with mood disorders (e.g. depression, bipolar disorder, etc.) has already suggested an increased temporal summation of pain in depressive patients (Klauenberg et al., 2008), leading us to believe that our results are not the consequence of a small sample size. Nevertheless, future studies should aim to replicate the increased spinal pain sensitization observed in MDD patients in larger samples.

3.4.2 NFR paradigm

The NFR is considered a reliable tool for pain assessment, yet only recently have studies employed the temporal summation of the NFR as a measure of central sensitization mechanisms in humans (Skljarevski & Ramadan, 2002; Terry et al., 2011). Consequently, there is no widely accepted consensus regarding the optimal administration parameters for this paradigm when assessing pain sensitization. In our study, we induced temporal summation once in each participant based on the method described by Lévesque et al. (2012). By doing so, we could not determine the reliability of the observations. It is difficult to justify, however, the repeated administration of a pain paradigm in a population that has been shown to report painful somatic symptoms at an elevated frequency (Bair et al., 2003; Corruble & Guelfi, 2000), and that may be hyperalgesic according to certain experimental studies (Potvin, 2011).

With the temporal summation paradigm as described in our study (20 stimulations at 1 Hz), administering the pain paradigm multiple times within one session would have most probably caused unnecessary discomfort to the participants. Furthermore, it is important to consider the higher probability of non-nociceptive contamination of the EMG signal when an elevated number of high-frequency stimulations are administered to an individual during one session (Terry et al., 2011). In the literature, there is a significant variation between studies in the number of high-frequency stimulations employed to reliably measure the temporal summation of the NFR. Notably, Lévesque et al. (2012) used a 40 second stimulation at a high-frequency to characterize the temporal summation of the experimental subjects over one testing session. Guirimand et al. (2000) used a 15 second stimulation at a high-frequency to elicit a temporal summation of the NFR, and administered the pain paradigm over two sessions separated by 7 days. Terry et al. (2011) were able to reliably measure a temporal summation of the NFR using only 5 high-frequency stimulations, and administered the paradigm five times in one session. Overall, if we would set out to determine the reliability of our main finding, we could arguably do so by administering short repeated periods of high-frequency stimulations in one testing session. This would probably be more tolerable for the participants, and we would obtain reliable measures of the temporal summation of the NFR response.

3.4.3 Medication

A further limitation of this experiment is the inclusion of MDD patients that were medicated with antidepressants at the time the pain paradigm was administered. Antidepressants have been found to display analgesic properties (Dharmshaktu et al., 2012), and in fact TCAs and SNRIs are recommended to treat neuropathic pain and other painful somatic symptoms in MDD patients (National Institute of Mental Health, 2015; Nicolson, 2010). The effect of the

medication on MDD patients could explain the failure to detect between-group differences in pain perception (i.e. pain threshold and sensitization of pain ratings). It is however notable that despite the known analgesic properties of antidepressant medications (Dharmshaktu et al., 2012) and their use in treating pain disorders related to central pain sensitization (e.g. fibromyalgia) (Goldenberg, 2007), as well as their inhibitory effect on the NFR in humans (Skljarevski & Ramadan, 2002), we measured a significantly increased sensitization of the NFR in depression. Indeed, the drug treatment of the depressive participants does not explain the main observation of this study, which suggests that spinal pain sensitization is increased in MDD. When taking into account the naturalistic qualities of this study, these results are all the more informative about the disorder. A majority of diagnosed MDD individuals are treated with antidepressants (Olfson et al., 2002), and our results propose that spinal pain sensitization in MDD might be altered even when medicated, a state that could predispose individuals suffering from this disorder to transition from acute to chronic pain (Weissman-Fogel et al., 2009). Nevertheless, future studies will need to replicate our main finding in a sample of drug-free patients with major depressive disorder.

3.5 Recommendation for future research

Recently, promising neurobiological models of MDD have focused on glutamatergic disturbances in the development and treatment of depression. Our results, which suggest overactive excitatory endogenous pain mechanisms in MDD, indirectly support the implication of the glutamatergic system in the pathophysiology of depression, as excitatory pain mechanisms are thought to be mediated by glutamate. In fact, pain facilitation as measured by temporal summation paradigms were shown to recruit NMDA glutamate receptors in dorsal horn neurons of both animals and humans (Dickenson & Sullivan, 1987;

Herrero et al., 2000; Price et al., 1994). Therefore, an increased spinal pain sensitization in MDD compared to healthy controls could be an indication of disrupted glutamatergic mechanisms in depression.

Speculations about the involvement of the glutamatergic system in the pathophysiology of depression come from studies in MDD patients showing increased levels of glutamate in the brain and altered expression of glutamate-related genes (Duric et al., 2013; Hashimoto, 2009; Hashimoto et al., 2007). Ketamine, an NMDA receptor antagonist, was found to exert therapeutic effect in MDD patients (Berman et al., 2000; Machado-Vieira et al., 2009; Maeng & Zarate, 2007). Preliminary studies showed ketamine infusions to have fast acting beneficial effect on suicidality/suicide ideation in treatment-resistant (Price et al., 2009), and emergency department MDD patients (Larkin & Beautrais, 2011). Furthermore, the antidepressant effect of a single dose of ketamine was found to be relatively long lasting (average time of relapse was approximately two weeks) (Ibrahim et al., 2012). The current concerns with using this drug as an antidepressant is that even at a low dose, it might induce mild visual hallucinations and dissociative effects in patients (Aan Het Rot et al., 2012). Furthermore, a major issue with ketamine is the susceptibility to develop dependence towards the substance with repeated use (Blier et al., 2012). Nonetheless, the beneficial effect of this NMDA antagonist in depressive patients reinforces the implication of glutamatergic mechanisms in the pathophysiology of MDD.

Ketamine was also shown to have an effect on central sensitization mechanisms. In fact, NMDA antagonists were found to influence synaptic transmission in the dorsal horn neurons of animals, by selectively inhibiting wind-up (Davies & Lodge, 1987). In healthy humans, low-doses of ketamine were found to reduced primary and secondary hyperalgesia,

which are clinical manifestations of central sensitization (Marchand, 2008), but did not have an effect on the participants' perception of pain (Ilkjaer et al., 1996). In a placebo controlled, randomized, double-blinded trial, Arendt-Nielsen et al. (1995) observed that a single low-dose ketamine injection (0.5 mg/kg) inhibited central temporal summation in healthy individuals, as measured by the NFR response. Likewise, Guirimand et al. (2000) reported a significant reduction in the NFR response and pain sensation during the temporal summation paradigm in healthy individuals when injected with low-dose ketamine, as well as unaffected NFR reflex threshold. Evidently, these suggest a selective inhibition of spinal pain sensitization by ketamine in healthy participants.

Ketamine is mainly known for its quick acting analgesic effect on acute pain (Maurset et al., 1989), whereas the effect of ketamine on central sensitization in chronic pain patients has been less documented. Given the dynamic nature of pain in chronic pain patients, the effect of ketamine might not be as consistent as in pain-free individuals (Skljarevski & Ramadan, 2002). Nevertheless, certain studies observed a prolonged analgesic effect of ketamine in chronic pain patients (Rabben et al., 1999). Furthermore, ketamine attenuated temporal summation in patients diagnosed with fibromyalgia, indicating that ketamine might inhibit central sensitization of dorsal horn neurons in chronic pain patients as well (Graven-Nielsen et al., 2000). In addition, no effect of ketamine on pain threshold was found in chronic pain patients (Graven-Nielsen et al., 2000), which could reflect the selective inhibition of spinal pain sensitization observed in pain-free individuals.

Currently, there are no experimental studies investigating the prophylactic effect of low-dose ketamine injections specifically in patients presenting comorbid chronic pain and depression. Still, there are few case studies showing encouraging results in oncology. Zanicotti

et al. (2012) and Stefanczyk-Sapieha et al. (2008) reported beneficial effects of ketamine as both an antidepressant and an analgesic in cancer patients suffering from MDD. The authors described that the patients became depressive as a consequence of the underlying medical condition, and that the patients felt significant improvement in their depressive symptoms and the pain experienced following ketamine injections. These observations, although noteworthy, remain circumstantial evidences of the efficacy of ketamine in treating patients with comorbid disorders. Overall, more in-depth experiments need to take place before drawing further conclusions about the application of ketamine and other NMDA receptor antagonists in the treatment of painful somatic symptoms in MDD patients.

Conclusion

In current study, we used an electrical pain paradigm to induce the temporal summation of the NFR response as well as the subjective pain response. To our knowledge, the present study is the first to evidence an increased spinal pain sensitization in MDD patients. Furthermore, we did not observe a sensitization of the subjective pain in MDD patients. These results suggest that the modulation of the nociceptive input in depression is already amplified at the spinal level. Future studies should seek to replicate these findings in larger samples of non-medicated MDD patients using repeated sessions of fewer high-frequency electrical pain stimulations to quantify more reliably the sensitization of the NFR response in depression. Furthermore, studies should aim to determine the predictive value of altered excitatory pain mechanisms in MDD with regards to the emergence of painful somatic symptoms in MDD. Finally, even though neurotransmitters were not measured in the current study, these preliminary results suggest that the increased spinal pain sensitization observed in MDD might potentially stem from altered glutamatergic mechanisms that may characterize this disorder. This hypothesis will need to be directly tested in future experiments. The growing interest in pharmacological treatment of major depressive disorder using ketamine makes such investigations even more relevant.

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